REMARKS

Overview

In the Office Action under reply, claims 1, 2, 4, 8, 11, and 38 were examined, claims 3, 5, 6, 9, 10, and 12-37 having been withdrawn and claims 7 and 27-29 having been canceled previously. The claims stand rejected as follows:

(1) claims 1, 2, and 8 remain rejected under 35 U.S.C. §102(b) as anticipated by Lorenzen et al., *J. Cell Bio.* (1995) 131:631-643 ("Lorenzen");

(2) claims 1 and 4 remain rejected under 35 U.S.C. §102(b) as anticipated by Olsson et al., *Biochim. Biophys. Acta* (1991) 1097:37-44 ("Olsson");

(3) claims 1, 2, 4, and 8 remain rejected under 35 U.S.C. §102(e) as anticipated by Mixson, U.S. Patent No. 7,070,807 ("Mixson");

(4) claims 1, 2, 4, 8, and 11 are rejected under 35 U.S.C. §102(b) as anticipated by Reimekasten, *J. Clin. Invest.* (1998) 102:754-763 ("Reimekasten");

(5) claim 38 is rejected under 35 U.S.C. §112, second paragraph, as indefinite;

(6) claims 1, 2, 4, 8, 11, and 38 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement;

(7) claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claim 1 of U.S. Patent No. 7,229,961 in view of Reimekasten;

(8) claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claims 1, 11, 12, 14, and 15-17 of U.S. Patent No. 6,593,292 in view of Reimekasten;

(9) claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claims 1-7 of U.S. Patent No. 6,730,293 in view of Reimekasten; and

(10) claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claims 1, 17, 18, 20, and 21 of U.S. Patent No. 6,669,951 in view of Reimekasten;

The rejections are traversed for at least the reasons set forth below.

Claim amendments

With the amendments made herein, claims 39 and 40 are added. Claim 39, dependent from claim 1 and reciting that the self-immolating linker covalently links the biologically active compound to the transport moiety, is supported, *inter alia*, by the original specification at page 2, lines 18-19. Claim 40, dependent from claim 1 and reciting that the linker moiety comprises a

nucleophile distal to the biologically active compound and a cleavable group proximal to the biologically active compound, is supported, *inter alia*, by the original specification at page 11, lines 22-25. No new matter is added by these new claims.

Rejection under 35 U.S.C. §102(b)

Claims 1, 2, and 8 remain rejected under 35 U.S.C. §102(b) as anticipated by Lorenzen.

Claim 1 is directed to a composition that includes a biologically active compound, a transport moiety comprising a structure of $(ZY)_nZ$, and a self-immolating linker moiety which linker moiety links the biologically active compound and the transport moiety.

In a communication to the PTO dated May 19, 2008 ("the May 2008 response"), applicants noted that Lorenzen does not disclose a self-immolating linker as required in claim 1. Applicants made the following comments in support of this statement:

> Lorenzen did not disclose a self-immolating linker moiety as provided by claim 1. In fact, the protein of Lorenzen is intact *in-vivo*, as the $p48^{TC}$ form of TCPTP was isolated from human peripheral T cells as the full length protein, including the region that the Examiner alleges to contain a self-immolating linker moiety. See Lorenzen, page 631, column 1, lines 19-22.
>
> If in fact the protein as represented in Figure 1 did contain a self-immolating linker moiety and transporter of claim 1, as asserted by the Office, the isolated protein of Figure 1 would not contain at least amino acid residues 377 and onward. The entire sequence of TCPTP, including residues R377, K378, R379, K380 and R381, was isolated, which indicates that the protein of Lorenzen did not contain a self-immolating linker moiety.
>
> Consequently, the Applicants contend that Lorenzen does not teach all of the elements of the rejected claims, a self-immolating linker moiety linking the biologically active compound and the transport moiety.

In responding to applicants' argument that Lorenzen does not disclose a self-immolating linking moiety, the Action states that "[t]he claim as recited does not indicate neither the 'nature of the linking moiety' in terms of 'structural features' associated with it nor the 'nature of the association (for e.g., covalent, ionic or hydrophobic)' of the linking moiety" (Action at 5-6). Applicants traverse this interpretation of the claims.

The rejection and comments in the Action imply that the Examiner is interpreting the claims to encompass any linker moiety, and that the term "self-immolating" is given no weight in the claims. The Examiner states that the definition provided in the specification is not to be read

into the claims, pursuant to MPEP § 2111.01. In fact, the MPEP states: "during examination the USPTO must give claims their broadest reasonable interpretation in light of the specification. This means that the words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification." (MPEP § 2111.01, underlining added.) According to the MPEP, therefore, it is improper for the Examiner to ignore the claim limitation of "self-immolating," regardless of whether or not the term is explicitly defined in the claims. All claim terms must be interpreted in light of the specification, and at the very least given their plain meaning (when not inconsistent with the specification).

The plain meaning[1] of "immolating" is not inconsistent with the specification, which provides that the term means cleaving, as in a bond (see specification at page 11, lines 21-27). Both the plain meaning and the definition in the specification indicate that the term "self-immolating" refers to a bond that is self-destructive. Accordingly, references that do not disclose a composition having a self-destructive linking moiety cannot be anticipatory of the pending claims.

As applicants' indicated in their communication dated May 19, 2008, in the Lorenzen reference, the Examiner states that an intron region meets the limitations of the claims, but does not explain how such a region is self-destructive. In fact, and as stated above, Lorenzen does not disclose a linker that is self-destructive.

The Examiner cites MPEP § 2111.01 as stating that "a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment." (See Action at 6.) Applicants agree that no particular embodiment should be read into the pending claims. However, interpreting the claims to require a self-destructive linker moiety merely (and properly) gives the claim terminology its appropriate weight in the claims; it does not improperly import a particular embodiment into the claims.

For at least the foregoing reasons, applicants submit that pending claims 1, 2, and 8, when all claim terms are interpreted in light of the specification (and/or given their plain meaning), are not anticipated by the disclosure of Lorenzen. Withdrawal of the rejection is respectfully requested.

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[1] Webster's Dictionary, available on-line at http://www.merriam-webster.com/, defines "immolating" as meaning "to kill or destroy."

Rejection under 35 U.S.C. §102(b)

Claims 1 and 4 remain rejected under 35 U.S.C. §102(b) as anticipated by Olsson. Applicants traverse the rejection.

The Action states that Olsson discloses RSRSRSRSR as well as chondroitin-6-sulfate, which allegedly satisfy the instant claim limitations of the structure $(ZY)_mZ$ and a biologically active compound, respectively.

In the May 2008 response, applicants stated that Olsson does not disclose a self-immolating linker moiety linking the biologically active compound and the transport moiety. (*See* the May 2008 response, page 14). In response, the Action states that "[t]he claim as recited does not indicate neither the 'nature of the linking moiety' in terms of 'structural features' associated with it nor the 'nature of the association (for e.g., covalent, ionic or hydrophobic)' of the linking moiety" (Action at 8).

As discussed above with respect to the rejection over Lorenzen, properly interpreting the instant claim limitations (in light of the specification and/or the plain meaning of all claim limitations) requires a biologically active compound and a transport moiety that are linked via a linking moiety having a self-destructive bond. Olsson makes no indication whatsoever that the peptide RSRSRSRSR is linked to chondroitin-6-sulfate via a linking moiety having a self-destructive bond. In fact, there is no indication whatsoever that the peptide and the chondroitin-6-sulfate are linked in any way. Instead, Olsson states "the optimal association of the peptides with chondroitin 6-sulfate is obtained with a minimal chain length of nine amino acids…" (Olsson, Abstract). Merely having an "association" between the peptide and chondroitin-6-sulfate does not mean that the two groups are linked via a linker moiety. In fact, the "association" mentioned in Olsson is likely to be via direct van der Waals interactions and/or hydrogen bonds. Even if, *arguendo*, recitation of an "association" were interpreted to mean that the peptide and chondroitin-6-sulfate were linked via a linker moiety, there is no indication that such a linker is self-destructive. Accordingly, Olsson does not disclose every limitation of the pending claims, and applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §102(e)

Claims 1, 2, 4, and 8 remain rejected under 35 U.S.C. §102(e) as anticipated by Mixson. Applicants traverse the rejection.

The Action states that Mixson discloses transport sequence $(RH)_4RG(RH)_4R$ and a pharmaceutical component, which allegedly satisfy the instant claim limitations of the structure $(ZY)_mZ$ and a biologically active compound, respectively. The Action further states that these components can interact by non-covalent or covalent interactions, which allegedly satisfies the instant claim limitation of a self-immolating linker moiety. The Action cites as an example a polymer:liposome:DNA complex.

As discussed above with respect to the rejection over Lorenzen, properly interpreting the instant claim limitations (in light of the specification and/or the plain meaning of all claim limitations) requires a biologically active compound and a transport moiety that are linked via a linking moiety having a self-destructive bond.

Mixson describes suitable covalent attachment groups as bonds formed by the reaction of -COOH of the polymer with either $-NH_2$ or -OH of the pharmaceutical agent or the reverse (*see* Mixson, col. 15, lines 30-44). Such a reaction would provide either an ester or an amide group. Such groups are not self-destructive groups, however; the direct linkage of a polymer with a pharmaceutical agent in this fashion therefore does not provide a material that includes a self-immolating linker moiety, a biologically active compound, and a transport moiety as recited in the instant claims. In fact, Mixson makes no indication whatsoever that the linking moieties described therein are self-destructive.

Regarding the specific example mentioned in the Action, there is no evidence to suspect that the liposome acts as a self-destructive linker moiety. In fact, Mixson describes the mechanism by which a liposome acts in the disclosure:

> A liposome is a compartment bounded by a lipid bilayer. Materials, such as DNA or protein, can be contained within a liposome, either in the liposome compartment, associated with the bilayer, or associated with the liposome exterior, and therapeutic materials can be delivered to the interior of a cell by endosomal uptake or by fusion of the agent-containing liposome with the cell membrane.

(Mixson, col. 2, lines 1-8, emphasis added.) According to this description, the polymer and the DNA complex of the example cited in the Action merely associate with one another inside the liposome. Such association is no more of a "linking" than would occur if the two components were simply mixed in the same flask. Indeed, if a polymer and a DNA complex were mixed in a flask, the flask would not be considered a "linking moiety." In the same way, the liposome of Mixson is not a linking moiety.

Even if, *arguendo*, the association of the polymer and the DNA complex within the liposome were interpreted to mean that the polymer and DNA complex were somehow linked via a linker moiety, there is no indication that such a linker is self-destructive. A liposome is merely a cell-like structure made of an amphiphilic material, and is not self-destructive as required by the instant claims. Accordingly, Mixson does not disclose every limitation of the pending claims, and applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §102(b)

Claims 1, 2, 4, 8, and 11 are rejected under 35 U.S.C. §102(b) as anticipated by Reimekasten. Applicants traverse this rejection.

The Action states that Reimekasten discloses $SmD1_{83\text{-}119}$ (i.e., VEPKVKSKKREAVA(GR)$_9$GGPRR) was coupled to keyhole limpet hemocyanin (KLH) by a disulfide linkage, and that this compound satisfies the limitations of the instant claims. Particularly, the Action states that "since the peptide is coupled to the biologically active moiety KLH via disulfide linkage, it is labile and is a self-immolating linkage" (Action at 17). This statement implies that the terms "self-immolating" and "labile" are interchangeable or equivalent.

In fact, the terms "self-immolating" and "labile" are not interchangeable or equivalent. A labile bond, such as a disulfide bond, is one that requires relatively little energy to be broken.[2] However, in most cases at room temperature, disulfide bonds are generally stable, indicating that some energy input (e.g., elevated temperature or radiation) is required to break such bonds. As described above with reference to the rejection over Lorenzen, a self-immolating linking moiety is one that is self-destructive. The disulfide bond, by itself, does not satisfy this limitation, since external input (e.g., in the form of energy or the like) is needed in order for the disulfide linkage to cleave. Furthermore, Reimekasten provides no indication whatsoever that the disulfide bond of the conjugate cited in the Action is/was cleaved in the experiments conducted therein. Therefore, Reimekasten fails to disclose any self-immolating linker moieties. Accordingly, applicants respectfully request withdrawal of the rejection.

[2] Indeed, all bonds can be broken given enough energy, and the distinction between a labile bond and a non-labile bond is completely arbitrary.

Rejection under 35 U.S.C. §112, second paragraph

Claim 38 is rejected under 35 U.S.C. §112, second paragraph, as indefinite. The Action states that "[i]t is unclear from the claim as recited claiming water to have pH of 7.4 in the absence of an alkali or buffer salt" (Action at 12). Applicants traverse this rejection.

The standard for definiteness is as follows:

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.
>
> In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent.

(MPEP § 2173.02.) Regarding instant claim 38, the claim is not indefinite because the skilled artisan would find the claim limitations to be reasonably clear and particular, and because clear warning is given as to what constitutes infringement.

It is standard procedure for those of skill in the art to which the present claims pertain to prepare water solutions having a variety of pH values. For example, the skilled artisan would understand that a variety of buffers are available to prepare such solutions. In addition to the knowledge common in the art, the instant specification describes example buffering agents on page 20, lines 27-29.

Claim 38 requires that the pH of the water in which the composition is tested (e.g., for infringement purposes) be 7.4. The claim does not indicate that the water has no other components, and the skilled artisan would understand that water having a pH of 7.4 would contain some sort of pH adjusting agent (such as a buffer). Given this common knowledge, it is unnecessary for the purposes of satisfying the definiteness standard to specify that water having a pH of 7.4 further contains a pH-adjusting agent. It would also be unnecessarily restrictive, as the claim is meant to include compounds that have the specified half-life in any water solution having a pH of 7.4, regardless of how such pH is obtained. Determination of infringement is not

obfuscated by the recitation of water at a pH of 7.4, since the skilled artisan would understand that the manner of obtaining such a water solution is immaterial to the claim.

For at least the foregoing reasons, the skilled artisan would not find the instant claim indefinite, and applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1, 2, 4, 8, 11, and 38 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicants traverse this rejection.

The standard for written description is provided in the MPEP: "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (MPEP § 2163(I)). The instant claims clearly satisfy this standard, particularly when the claims are read in light of the specification.[3]

The Action states that "[t]he claim as recited does not adequately define how the three components of the composition interact with other in the composition, i.e., whether the components a, b and c are covalently attached to each other, or the interaction between them is ionic, hydrophobic, or hydrogen bond interaction" (Action at 13). In light of the specification and the standard for written description, however, it is not necessary for the claims to define such interaction. The specification makes it abundantly clear that the biologically active agent, the transport moiety, and the self-immolating linker are linked via covalent bonds. For example, the specification states: "[t]he linking moiety is preferably cleaved *in vivo*. 'Cleaved' in this case refers to separation of a linking moiety terminus from the biologically active agent. The separation is effected through dissociation of a covalent bond." (original specification, page 11, lines 12-14). As a further example, the specification states: "[t]hus, the transport moiety… has a carboxy terminus and an amino terminus. One of the termini is either covalently attached to a biologically active compound (R^1) or, alternatively, to a linking moiety (L) that is part of a linking moiety-active compound conjugate (e.g., R^1–L)." (original specification, page 9, lines 22-26). The specification also indicates a number of groups that are suitable for forming the

[3] It is proper to consider the specification when evaluating whether the claims satisfy the written description: "[i]t is now well accepted that a satisfactory description may be in the claims or any other portion of the originally filed specification" (MPEP § 2163(I)).

linkages. These groups include covalent linkages formed from alcohols, carboxylic acids, amines, and thiols (*see* original specification, page 11, lines 3-11).

Therefore, based on the types of bonds that are described as suitable, as well as the methods of cleavage described in the specification, the skilled artisan would fully understand that covalent linkages are required of the three components recited in the claims. Recitation of covalent linkages is unnecessary to satisfy the standard for written description.

The Action further states that "[t]he claim as recited does not provide a partial or compete structural features of the composition where the biologically active compound is linked to the transport moiety by self-immolating linking moiety" (Action at 13). Applicants response is twofold: (a) structural features of the claimed compositions are, in fact, present in the claims; and (b) structural features in addition to what is currently present are unnecessary to satisfy the written description requirement.

Regarding (a), the instant claims do, in fact, include structural features where necessary to describe the claimed invention. Claim 1 includes the recitation that the transport moiety comprises a structure of $(ZY)_nZ$. Regarding the biologically active compound, no structure is given in the claim because any such structure would be unnecessarily limiting. The specification describes a large number of suitable biologically active compounds, for example, at page 10, lines 1-29. From this disclosure and from the knowledge common in the art, the skilled artisan would be capable of determining whether a particular structure falls within the scope of the claims. This is similarly true for the linking moiety, for which a detailed disclosure is provided in the specification (*see* original specification, page 11 line 3 to page 18, line 25). Such disclosure is sufficient for the skilled artisan to conclude that the applicants had possession of the claimed invention.

Regarding (b), structural features are not required to satisfy the written description requirement:

> "[a]n applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613.

(MPEP § 2163(II)(A)(3)(a).) The instant claims provide both structure (i.e., the transport moiety) and functional characteristics (i.e., the biologically active compound and the linker). The

functional characteristics provided in the claim have known correlations between function and structure that are sufficient for the skilled artisan to conclude that applicants had possession of the invention at the time of the application. This is particularly true in light of the specification, which provides a large amount of guidance regarding the identity of the linking group and of the biologically active compound. For example, in addition to the passages cited above,

Regarding the biologically active agent, the Action acknowledges that numerous examples are provide, and that the specification describes a wide variety of compounds, but states that "[t]he examples provided in the specification do not adequately support the claimed invention commensurate with the scope of the claim as recited" (Action at 14). This conclusion is not supported by any reasoning that would cast doubt on the applicants' disclosure. Without such reasoning, the Action fails to meet the burden to question written description:

> The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *Wertheim*, 541 F.2d at 262, 191 USPQ at 96

(MPEP § 2163(II)(A).) The Action objects to the breadth of the claims, but provides no satisfactory evidence that would support such an objection.

In summary, there is nothing inherently problematic with providing functional characteristics in lieu of structural limitations in a claim. The standard for adequate written description remains whether the skilled artisan would conclude that applicants had possession of the invention at the time of the application, and the claims must be considered in light of the specification. Given the large amount of guidance in the specification, and the knowledge generally available in the art, the present claims satisfy the standard for written description. Furthermore, the Action fails to meet the burden for questioning applicants' disclosure and the breadth of the claims. For at least these reasons, withdrawal of the rejection is respectfully requested.

Obviousness-Type Double Patenting Rejection

Claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claim 1 of U.S. Patent No. 7,229,961 in view of Reimekasten. Without conceding the validity of the rejection, and in order to expedite prosecution, applicants are filing a Terminal

Disclaimer over the abovementioned U.S. Patent. The Terminal Disclaimer meets all requirements of 37 C.F.R. §1.321(b), and, accordingly, applicants respectfully request withdrawal of the rejection.

Obviousness-Type Double Patenting Rejection

Claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claims 1, 11, 12, 14, and 15-17 of U.S. Patent No. 6,593,292 in view of Reimekasten. Without conceding the validity of the rejection, and in order to expedite prosecution, applicants are filing a Terminal Disclaimer over the abovementioned U.S. Patent. The Terminal Disclaimer meets all requirements of 37 C.F.R. §1.321(b), and, accordingly, applicants respectfully request withdrawal of the rejection.

Obviousness-Type Double Patenting Rejection

Claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claims 1-7 of U.S. Patent No. 6,730,293 in view of Reimekasten. Without conceding the validity of the rejection, and in order to expedite prosecution, applicants are filing a Terminal Disclaimer over the abovementioned U.S. Patent. The Terminal Disclaimer meets all requirements of 37 C.F.R. §1.321(b), and, accordingly, applicants respectfully request withdrawal of the rejection.

Obviousness-Type Double Patenting Rejection

Claims 1 and 11 are rejected under the judicially created doctrine of double patenting over claims 1, 17, 18, 20, and 21 of U.S. Patent No. 6,669,951 in view of Reimekasten. Without conceding the validity of the rejection, and in order to expedite prosecution, applicants are filing a Terminal Disclaimer over the abovementioned U.S. Patent. The Terminal Disclaimer meets all requirements of 37 C.F.R. §1.321(b), and, accordingly, applicants respectfully request withdrawal of the rejection.

Common ownership

The Action states "[a] showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based

upon the commonly assigned case" (Action at page 22). Applicants acknowledge that the instant application and US Patent Nos. 6,593,292, 6,730,293, 6,669,951, and 7,229,961 were commonly owned at the time the invention of the instant application was made.

CONCLUSION

Applicants submit that the claims of the application are in condition for allowance. Applicants respectfully request withdrawal of the rejections, and prompt issuance of a notice of allowance. If the Examiner has any questions concerning this communication, or would like to discuss the application, the art, or other pertinent matters, a telephone call to the undersigned would be welcomed.

Respectfully submitted,

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